UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/508,658	11/03/2000	Kai Krohn	U 012653-9	3972

7590 03/25/2005

Ladas & Parry
26 West 61st Street
New York, NY 10023

EXAMINER	
SITTON, JEHANNE SOUAYA	
ART UNIT	**PAPER NUMBER**
1634	

DATE MAILED: 03/25/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/508,658	KROHN ET AL.	
	Examiner	Art Unit	
	Jehanne S. Sitton	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 November 2000*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-24* is/are pending in the application.

4a) Of the above claim(s) *5-22 and 24* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *1-4 and 23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-24* are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *3/2000*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Restriction is required under 35 U.S.C. 121 and 372.

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1.

In accordance with 37 CFR 1.499, applicant is required, in reply to this action, to elect a single invention to which the claims must be restricted.

Group 1, claim(s) 1-4 and 23 (in part), drawn to drawn to nucleic acids.

Group 2, claim(s) 5-8, drawn to polypeptides.

Group 3, claim(s) 9-15 and 19, drawn to methods of detecting nucleic acids.

Group 4, claim(s) 16-18 and 20, drawn to methods of detecting proteins.

Group 5, claim(s) 21-22, drawn to methods of gene therapy.

Group 6, claim(s) 23 (in part) and claim 24, drawn to antibodies.

2. The inventions listed as Groups 1-6 do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: the claims of group 1 are drawn to variants and functional fragments of SEQ ID NO: 1 which is taught in the art as set forth in the rejections under 35 USC 102(b) below. Additionally, the claims are drawn to structurally and functionally distinct products, and methods of using such products, which lack a corresponding special technical feature.

3. Additionally, each group named above is subject to further restriction. Applicant is required to further elect a specific variant of SEQ ID NO: 1 (or SEQ ID NO: 2) for examination along with SEQ ID NO: 1 or 2 (depending on which group is elected). This is NOT an election of species. Nucleotide sequences encoding different proteins are structurally distinct chemical compounds and are unrelated to one another. These sequences are thus deemed to normally

constitute independent and distinct inventions within the meaning of 35 U.S.C. 121. Absent evidence to the contrary, each such nucleotide sequences are presumed to represent an independent and distinct invention, subject to restriction requirement pursuant to 35 USC 121 and 37 CFR 1.141. By statute, "[i]f two or more independent and distinct inventions are claimed in one application, the Commissioner may require the application to be restricted to one of the inventions." 35 U.S.C. 121. Pursuant to this statute, the rules provide that "[i]f two or more independent and distinct inventions are claimed in a single application, the examiner in his action shall require the applicant... to elect that invention to which his claim shall be restricted." 37 CFR 1.142 (a). See also 37 CFR 1.141(a). It is noted that searching more than one of the claimed patentably distinct sequences represents a serious burden for the office.

4. The examiner has required restriction between product and process claims. Where applicant elects claims directed to the product, and a product claim is subsequently found allowable, withdrawn process claims that depend from or otherwise include all the limitations of the allowable product claim will be rejoined in accordance with the provisions of MPEP § 821.04. **Process claims that depend from or otherwise include all the limitations of the patentable product** will be entered as a matter of right if the amendment is presented prior to final rejection or allowance, whichever is earlier. Amendments submitted after final rejection are governed by 37 CFR 1.116; amendments submitted after allowance are governed by 37 CFR 1.312.

In the event of rejoinder, the requirement for restriction between the product claims and the rejoined process claims will be withdrawn, and the rejoined process claims will be fully examined for patentability in accordance with 37 CFR 1.104. Thus, to be allowable, the rejoined

claims must meet all criteria for patentability including the requirements of 35 U.S.C. 101, 102, 103, and 112. Until an elected product claim is found allowable, an otherwise proper restriction requirement between product claims and process claims may be maintained. Withdrawn process claims that are not commensurate in scope with an allowed product claim will not be rejoined. See "Guidance on Treatment of Product and Process Claims in light of *In re Ochiai, In re Brouwer* and 35 U.S.C. § 103(b)," 1184 O.G. 86 (March 26, 1996). Additionally, in order to retain the right to rejoinder in accordance with the above policy, Applicant is advised that the process claims should be amended during prosecution either to maintain dependency on the product claims or to otherwise include the limitations of the product claims. **Failure to do so may result in a loss of the right to rejoinder.**

5. During a telephone conversation with Janet Cord on December 23, 2004 a provisional election was made with traverse to prosecute the invention of Group 1, claims 1-4, and 23, in part, directed to SEQ ID NOS 1 and 3. Affirmation of this election must be made by applicant in replying to this Office action. Claims 5-22, 24, and portions of claim 23 drawn to polypeptides are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

6. Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Specification

7. The specification is objected to for the following:

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth below. See chapter 2400 of the MPEP.

The response filed 1/21/2003 appears to have added SEQ ID NOS for the peptides listed in Figure 5. In doing so, the new SEQ ID NOS (of which there are only 7) replaced a substantial portion of the previous Sequence listing which contained all the other sequences set forth in the instant application. Accordingly, the new version of the sequence listing as of 1/21/2003 does not provide a complete list of all sequences disclosed in the specification and fails to comply with the requirements set forth above. Applicant is required to submit a complete sequence listing in written form as well as computer readable form, along with a statement that no new matter has been incorporated. It is further noted that applicant's should take care to amend the specification to properly designate sequences with appropriate identifiers. For example, the description to figure 5 in the "Brief description of the drawings" now references the new incomplete sequence listing. The examiner discovered the discrepancy in sequence listings when trying to search SEQ ID NO: 3, which the claims set forth as a nucleic acid, but the new version sets forth as a peptide. The claims have been searched with regard to the old sequence listing, therefore SEQ ID NOS 1 and 3 have been searched as nucleic acids. Failure to comply with these requirements will render any subsequent amendment as "Non Compliant".

Claim Rejections - 35 USC § 112

8. Claims 1-4 and 23 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an isolated nucleic acid molecule comprising SEQ ID NO: 1, does not reasonably provide enablement for nucleic acids encoding functional fragments, variants, and nucleic acids characterized in that they are associated with APECED and include a gene defect responsible for APECED, and sequences hybridizable thereto. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims. It is further noted that while the specification is enabling for making an isolated nucleic acid molecule comprising SEQ ID NO: 1, the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

There are many factors to be considered when determining whether there is sufficient evidence to support determination that a disclosure does not satisfy the enablement requirements and whether any necessary experimentation is undue. These factors have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The claims are drawn to broadly drawn to nucleic acids from any source which encoding functional fragments and variants of SEQ ID NO: 1 and nucleic acids characterized in that they

are associated with APECED and include a gene defect responsible for APECED, and sequences hybridizable thereto. The claims encompass sequences from any source including variants of SEQ ID NOS 1 and 3 which contain any insertion, deletion or missense mutation, which have not been taught in the specification.

The specification teaches that SEQ ID NO: 1 is a gene encoding a protein associated with Autoimmune polyglandular syndrome type I (APS I), also known as autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED). The specification teaches that this protein is known in the art as AIRE (encoded by SEQ ID NO: 1). The specification further teaches finding 2 splice variants of this protein, AIR-2 and AIR-3 were found. It is unclear which nucleic acids encode AIR 2 and AIR 3. The specification teaches that mutations were found in AIR 1, exon 2: K42E, and exon 6: R257X in 2 patients, respectively, with APECED but not in healthy controls. The specification, however, teaches that no mutations were found in either AIR2 or AIR3. The specification teaches that AIR 1 has certain domains found in other proteins, such as two PHD finger motifs, a proline rich region, and an LXXLL motif (see page 9). The specification, however, does not teach or demonstrate the specific functions or biological activity for the AIR1, the protein encoded by SEQ ID NO: 1.

At the time the invention was filed, the prior art was silent with respect to the function for the protein encoded by SEQ ID NO: 1. Neither the art nor the specification provide any assay for detecting or assaying the function of such proteins. Even the postfiling date art of Su (Su et al; Current Opinion in Immunology, vol. 16, pp 746-752, 2004) teaches that the molecular mechanisms by which AIRE functions are not well understood (see abstract). Su teaches that while Aire appears to have a role in central tolerance by upregulating the expression of organ

specific antigens in the thymus, several key questions remain regarding this mechanism, including on the molecular level (see page 750, col. 2). Further, while the post filing date art teaches of additional mutations in Aire (see Aaltonen et al; Nature Genetics, vol. 17, 1997, pp 399-403), the mutations in Aire taught by Aaltonen all result in prematurely truncated proteins. Aaltonen teaches that silent C to T polymorphisms were found in the nucleic acid sequence. These polymorphisms do not seem to be associated with disease. Aaltonen does not provide any guidance as to which missense mutations would be predictably correlated with disease, nor which portions of the protein are required for loss of function mutations which would be associated with disease

The specification does not teach a function for the protein encoded by SEQ ID NO: 3, and teaches that mutations found for Air1 were not found in the splice variants. Accordingly, the specification has not taught one of skill in the art how to use the Sequence of SEQ ID NO: 3.

Additionally, the claims are not enabled for nucleic acids encoding "functional fragments" of the claimed polypeptide, variants with the same functional activity, or functionally equivalent isolated DNA sequences hybridizable thereto. The specification has taught a polypeptide of SEQ ID NO: 2, however the specification has not the activity or function of the polypeptide, nor where and how to modify the polypeptide to produce a protein or variant with the same functionality. The specification has not taught which portions of a putative polypeptide would be associates with "diseases related to immune maturation and regulation of immune response towards self and nonself" or APECED. The instant claims are drawn to undisclosed sequences encoding *any* modification that have not been contemplated. While the specification teaches the amino acid sequence of SEQ ID NO: 2, one sequence does not enable a genus of polypeptide molecules based on the limited information disclosed in instant

application. Therefore, the skilled artisan would be required to perform undue experimentation to identify any polypeptide which was a functional fragment of the polypeptide encoded by SEQ ID NO: 1, or variants with the same functional activity, or functionally equivalent isolated DNA sequences hybridizable thereto. The skilled artisan would have no way of knowing which nucleic acid sequences encoded functional fragments or variants of SEQ ID NO: 2 because the specification does not provide a description of the nucleotide or amino acid sequences which constitute these functional fragments and variants. The skilled artisan would be required to perform manipulations and extensive modification of the protein to determine where and how to make modifications to determine which fragments of the polypeptide were responsible for its activity.

The claims additionally encompass nucleic acids which encode variants of SEQ ID NO: 1 which include a gene defect responsible for APECED. The specification has only taught 2 mutations which are associated with APECED. Neither the specification nor the art teach which regions of the encoded polypeptide are required for the activity or function of the polypeptide encoded by SEQ ID NO: 1. While the specification sets forth domains and motifs included within this polypeptide, as acknowledged by the specification, such domains are found in a large number of unrelated proteins, which have no association with diseases related to immune maturation and regulation of immune response towards self and nonself" or APECED. Neither the specification nor the art at the time of filing provide a universal correlation between any mutation or polymorphism in SEQ ID NO: 1 and a predictable diagnosis of APECED. Therefore, the skilled artisan would be required to perform undue experimentation to identify which mutations were responsible for APECED. The skilled artisan would be required to

perform manipulations and extensive modification of the protein to determine where and how to make modifications to determine which mutations were responsible for disease.

Thus given the broad claims in an art whose nature is identified as unpredictable, the unpredictability of that art, the large quantity of research required to define these unpredictable variables, the lack of guidance provided in the specification, the absence of a working example and the negative teachings in the prior art balanced only against the high skill level in the art, it is the position of the examiner that it would require undue experimentation for one of skill in the art to perform the method of the claim as broadly written.

Indefinite

9. Claims 2 and 23 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Regarding claim 2, the phrase "such as" renders the claim indefinite because it is unclear whether the limitations following the phrase are part of the claimed invention. See MPEP § 2173.05(d).

Claim 23 is indefinite because it is unclear if the phrase "characterized by comprising..." refers to the claimed reagent, or the DNA it reacts with. Accordingly, the metes and bounds of the claim are unclear.

Claim Rejections - 35 USC § 102

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

11. Claims 1, 2, 4, and 23 are rejected under 35 U.S.C. 102(b) as being anticipated by Genbank accession number X80853 (April 1996).

Genbank accession number X80853 teaches a sequence which comprises a region which is identical to nucleotides 1701-2036 of SEQ ID NO: 1 and 1210-1545 of SEQ ID NO: 3. As the claims do not make clear what "function" is encompassed, the accession number inherently comprises some functional fragment. With regard to claims 1 and 4, the recitation of "characterized by" by has been broadly interpreted to encompass sequences comprising portions of the recited SEQ ID NOS. As the Accession number comprises over 300 nucleotides of SEQ ID NO: 1, this fragment is inherently associated with "diseases related to immune maturation and regulation of immune response towards self and non self".

12. Claims 1, 2, 4, and 23 are rejected under 35 U.S.C. 102(b) as being anticipated by Kim (Kim et al; PNAS, vol. 93, pages 15299-15304, 1996).

Kim teaches a nucleic acid sequence which contains a PHD finger and is thus considered a variant of SEQ ID NO: 1 encoding a protein having the same functional activity. As the claim does not recite what "functional activity" is encompassed, the recitation of a PHD finger domain, which is found in SEQ ID NO: 1, is broadly interpreted as "same functional activity". With

regard to claims 1 and 4, the recitation of "characterized by" by has been broadly interpreted to encompass sequences comprising portions of the recited SEQ ID NOS. As the sequence of Kim comprises common domains with SEQ ID NO: 1 (see page 15302, col. 2, fig 2), association with "diseases related to immune maturation and regulation of immune response towards self and non self" is considered a property of the sequence taught by Kim.

13. Claims 1-4 and 23 are rejected under 35 U.S.C. 102(b) as being anticipated by Brennan (US Patent 5,474,796).

Brennan teaches constructing all possible 10 mer nucleic acid sequences (see cols. 9 and 10). The nucleic acid sequences of Brennan are fragments of both SEQ ID NOS 1 and 3. As the claim does not recite what "functional activity" is encompassed, fragments within these SEQ ID NOS are broadly interpreted as having the "same functional activity". With regard to claims 1 and 4, the recitation of "characterized by" by has been broadly interpreted to encompass sequences comprising portions of the recited SEQ ID NOS. As the fragments within these SEQ ID share common domains with SEQ ID NO: 1 (see page 15302, col. 2, fig 2), association with "diseases related to immune maturation and regulation of immune response towards self and non self" is considered a property of the sequences taught by Brennan. Additionally, the sequences taught by Brennan will inherently represent sequences which comprise a gene defect (ie a mutation) that is responsible for APECED.

Conclusion

14. No claims are allowable over the cited prior art. SEQ ID NOS 1 and 3 are free of the cited prior art. It is noted that a claim reciting "an isolated nucleic acid molecule comprising the

sequence of SEQ ID NO: 1" would be allowable. It is further noted that the specific mutations in SEQ ID NO: 1, resulting in K42E and R257X appear to be free of the prior art.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jehanne Sitton whose telephone number is (571) 272-0752. The examiner can normally be reached Monday-Thursday from 8:00 AM to 5:00 PM and on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (571) 272-0745. The fax phone number for this Group is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Jehanne Sitton

Jehanne Sitton
Primary Examiner
Art Unit 1634
3/21/05